BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 51 (1), 174—178 (1978)

Aluminum Chloride Catalyzed Friedel-Crafts Reaction of Anisole with Epoxide Accompanying Isomerization[1]

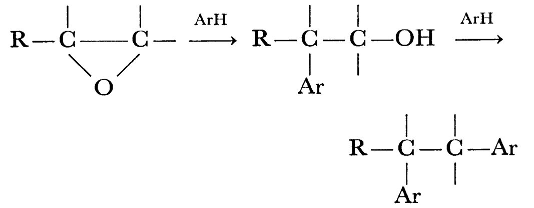
Masashi Inoue, Toshio Sugita, and Katsuhiko Ichikawa*

Department of Hydrocarbon Chemistry, Faculty of Engineering, Kyoto University, Yoshida, Kyoto 606

(Received February 24, 1977)

The reaction of anisole with propylene oxide by aluminum chloride has been studied in various kinds of solvents. While the normal Friedel-Crafts reaction yielded 2-(methoxyphenyl)-1-propanols, 1,1-bis(methoxyphenyl)-propanes were also formed in this reaction; these were not obtained by the subsequent reaction of mono(methoxyphenyl) products with another anisole. The yields of 1,1-bis(methoxyphenyl)propanes increased by increasing the basicity of solvents. The mechanism of the formation of 1,1-bis(methoxyphenyl)propanes can be explained by the isomerization of epoxide to aldehyde and the subsequent condensation with anisole. Various kinds of epoxides also gave 1,1-bis(methoxyphenyl)alkanes in nitromethane.

It is generally believed that Friedel-Crafts reactions of aromatic substrates with epoxides produce *β*-hydroxyarylalkanes which react further with aromatics to give 1,2-diarylalkanes.[2]



During the course of the study of solvent effects on the ring-opening reaction of epoxide with aluminum chloride,[3] we found, however, that the reaction of propylene oxide with anisole by aluminum chloride yielded 1,1-bis(methoxyphenyl)propanes (**1**) without any contamination of the 1,2-isomers (**2**). In order to clarify the mechanism, the reaction of various epoxides with anisole has been studied in various solvents.

The reaction of propylene oxide and anisole without solvent at 0—2 °C gave a complex mixture containing at least eight compounds: 2-chloro-1-propanol (**3**, 24 %), 1-chloro-2-propanol (**4**, 8%), 2-(*o*- and *p*-methoxyphenyl)-1-propanols (**5**, 17%), 1-phenoxy-2-propanol (**6**, 4%), and three isomers (*o,o*-, *o,p*-, and *p,p*-) of 1,1-bis(methoxyphenyl)propanes (**1**, 24%). The first two are the ring-opening products of the epoxide; their isomer distribution and stereochemistry have been discussed previously.[3] The mechanism of the formation of **5**, a normal Friedel-Crafts reaction product of propylene oxide, is considered to be of the S_N2 type analogous to the reported case of benzene.[4] In this paper, however, we are concerned mainly with the formation of **1**.

Table 1 shows the results of the reaction of propylene oxide with anisole in various solvents. For experimental convenience, the yields of the products which did not include methoxyphenyl moiety were not determined. The other products were chloropropanols, oligomers of the epoxide, and high boiling tarry matter. The characteristic features of the results are as follows. When 1,2-dichloroethane was used as a solvent, changes in the reaction conditions resulted in only minor changes in the product distributions. The formation of **2** was not observed in any experiments except one at a higher temperature (32—34 °C). The yield of **1** increased in the following order of the solvents: hexane<chloroform<1,2-dichloroethane<anisole<nitromethane.

Table 1. Effects of the solvent on the reaction of propylene oxide with anisole[a]

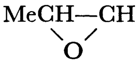
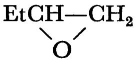
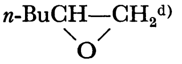
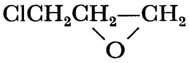
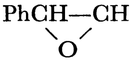
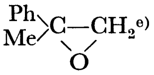
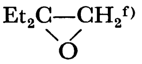
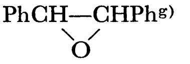
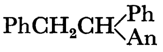
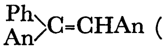
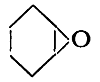
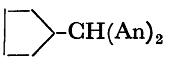
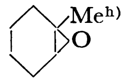
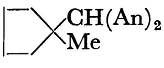
Solvent	Yield of **5** %	Yield of **1** %	Isomer distribution in **1**		
			o,o- %	*o,p*- %	*p,p*- %
$ClCH_2CH_2Cl$[b]	8.3	11.3	1.3	24.4	74.3
$ClCH_2CH_2Cl$	5.8	13.4	1.2	24.1	74.5
$ClCH_2CH_2Cl$[c]	7.4	13.0	0.6	26.5	72.9
$ClCH_2CH_2Cl$[d]	5.5	11.7	1.0	24.0	75.0
$ClCH_2CH_2Cl$[e]	10.9	19.3	1.5	27.5	71.0
$ClCH_2CH_2Cl$[f]	6.1	8.4	0.5	20.0	79.5
$ClCH_2CH_2Cl$[g]	7.2	14.7	1.0	22.3	76.7
$ClCH_2CH_2Cl$[h]	4.1	16.2	1.0	26.4	72.6
$ClCH_2CH_2Cl$[i]	2.5	14.9	(mixture of **1** (80%) and **2** (20%))		
$CHCl_3$	3.2	6.4	1.1	22.7	76.2
$CH_3(CH_2)_4CH_3$	1.3	0.6	1.8	13.2	85.0
CH_3NO_2	0.0	25.8	0.7	12.3	87.0

a) Unless otherwise mentioned, 40 ml of solvent, 20 mmol of epoxide, 40 mmol of anisole, and 20 mmol of aluminum chloride were used. Reaction temperature and time were 0—2 °C and 3.5 h, respectively. b) Reaction time, 1.0 h. c) Reaction time, 6 h. d) Anisole, 20 mmol. e) Anisole, 200 mmol. f) Aluminum chloride, 10 mmol. g) Aluminum chloride, 40 mmol. h) Aluminum chloride, 60 mmol. i) Reaction temperature, 32—34 °C.

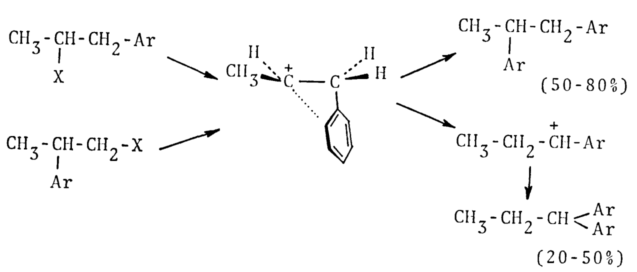
In nitromethane, **1** was obtained in a good yield but no mono(methoxyphenyl) products were detected. This result forms a striking contrast to the fact that benzene does not react with propylene oxide in this solvent.[4] Therefore, the reaction of various epoxides with anisole was examined. Results are summarized in Table 2.

One of the possible routes to **1** is the successive reaction of **5** with another anisole. The literature contains a number of papers on the Friedel-Crafts type alkylation of aromatics with 1,2-difunctional propanes including propylene oxide which gave 1,2-diarylpropanes,[5] while a few papers have reported the formation of 1,1-diarylpropanes as by-products.[6] Masuda *et al.* explained the formation of 1,1-diphenylpropane (minor product) in the reaction of 1-phenyl-2-chloropropane and 2-phenyl-1-chloropropane with benzene in terms of an isomerization from a phenonium ion type inter-

Table 2. Products of the reaction of various epoxides with anisole (AnH) by aluminum chloride in nitromethane[a)]

	Epoxide	Product	Isomer distribution in bis(methoxyphenyl) derivatives[b)]		
			o,o-	*o,p-*	*p,p-*
1	 $\underset{O}{\mathrm{MeCH{-}CH_2}}$	$\mathrm{EtCH(An)_2}$ (**1**, 28%)	1.4	24.8	73.8
2	 $\underset{O}{\mathrm{EtCH{-}CH_2}}$	$\mathrm{PrCH(An)_2}$ (**9**, 33%)	1.7	24.8	73.5
3	 $\underset{O}{n\text{-}\mathrm{BuCH{-}CH_2}}$[d)]	$\mathrm{CH_3(CH_2)_4CH(An)_2}$ (**10**, 32%)	2.5	23.3	74.2
4	 $\underset{O}{\mathrm{ClCH_2CH_2{-}CH_2}}$	None			
5	 $\underset{O}{\mathrm{PhCH{-}CH_2}}$	$\mathrm{PhCH_2CH(An)_2}$ (**11**, 46%)	2.6	25.0	72.4
6	 $\underset{O}{\mathrm{{}^{Ph}_{Me}{>}C{-}CH_2}}$[e)]	 $\mathrm{{}^{Ph}_{Me}{>}CHCH(An)_2}$ (**12**, 76%)	0.7	22.2	77.1
7	 $\underset{O}{\mathrm{Et_2C{-}CH_2}}$[f)]	$\mathrm{Et_2CHCH(An)_2}$ (**13**, 40%)	2.3	18.2	79.5
8	 $\underset{O}{\mathrm{PhCH{-}CHPh}}$[g)]	$\mathrm{Ph_2CHCH(An)_2}$ (**14**, 56%)[c)]	2.2	24.7	73.1
		 $\mathrm{PhCH_2CH{<}^{Ph}_{An}}$ (**15**, 11%)			
		 $\mathrm{{}^{Ph}_{An}{>}C{=}CHAn}$ (**16**, 10%)			
9		 (**17**, 17%)	0.7	23.0	76.3
		 (**18**, 8%)			
10	 [h)]	 (**19**, 5%)	0.9	22.6	76.5

a) Reactions were conducted with anisole (100 mmol) and $\mathrm{AlCl_3}$ (40 mmol) in nitromethane (40 ml), and the epoxide (20 mmol) in nitromethane (20 ml) at 0—2 °C, the mixtures were homogeneous. Isolated yields given in parentheses were calculated on the basis of the epoxides used. b) Calcd from GLPC. c) The possibility of contamination of 1,2-bis(methoxyphenyl)-1,2-diphenylethane cannot be excluded. d) bp 117—118 °C (lit,[15a)] bp 116—119 °C). e) bp 98—100 °C/33 mmHg (lit,[15b)] bp 71 °C/10 mmHg). f) bp 105—106 °C (lit,[15c)] bp 105—107 °C). g) mp 68—69 °C (lit,[15d)] mp 68.5—69 °C). h) bp 72—74 °C/105 mmHg (lit,[15e)] bp 137—138 °C).



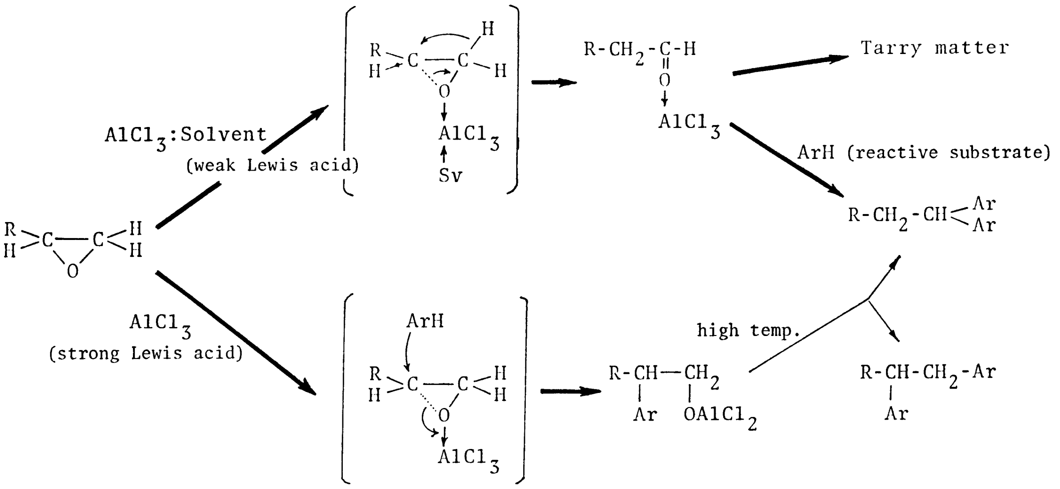
Scheme 1.

mediate to 1-phenyl-1-propyl cation on the basis of stereochemical results.[7,8]

To examine this reaction sequence, **5** was subjected to react with excess anisole in the presence of aluminum chloride at 0—2 °C. The predominant product was **2** (80%), and **1** was only a minor one (20%). Although the data may not reflect exactly the path of the reaction of propylene oxide with anisole, since hydrogen chloride is produced in the reaction of **5** with aluminum chloride to form the assumed precursor, dichloroaluminum 2-(methoxyphenyl)propoxide, it can be concluded that the main route to **1** is different from this reaction sequence, since the hydride shift from the phenonium type ion to 1-aryl-1-propyl cation is not affected by the leaving groups of the precursors of the carbonium ion.[8]

Possible routes for the formation of **1** are shown in Scheme 2, in which R is methyl and Ar is methoxyphenyl or phenyl. Isomerization from epoxide to aldehyde, followed by condensation with anisole, leads to **1**. The isomerization competes with the normal Friedel-Crafts reaction and the aldehyde condensation with anisole competes with the formation of tarry matter *via* aldol condensation, Tischenko reaction, and so on.

It is well known that epoxide forms aldehyde under the catalysis of magnesium bromide, zinc chloride, and boron trifluoride–ether complex.[10] These catalysts are weak Lewis acid as compared with aluminum chloride. The acidity of aluminum chloride dissolved in nitromethane is lower than those in the other usual solvents for Friedel-Crafts reactions, since nitromethane is a



Scheme 2.

stronger base than the other solvents. The activity of the catalyst becomes low, and benzene does not react with propylene oxide in this solvent. When more reactive anisole was used as a substrate, the isomerized aldehyde condenses with anisole to form **1**. As the basicity of the solvents increases in the order mentioned above, the solvent effects on the formation of **1** can be explained along the same line.

Although the condensation of aldehyde with aromatics is well known,[11] no detailed study of the reaction with aluminum chloride catalyst has appeared to our knowledge. The reaction of propionaldehyde with anisole in 1,2-dichloroethane at 0—2 °C in the presence of aluminum chloride gave **1** as a main product (59%), accompanied with 1,1-bis(methoxyphenyl)propenes (**7**, 13%) and 1-methoxyphenylpropanes (**8**, 20%). The formation of the latter two products shows that hydrogen transfer took place, this will be discussed in a separate paper.

The results shown in Table 2 are also well consistent with the mechanistic paths mentioned in Scheme 2. The products in runs 8, 9, and 10 indicate that phenyl and alkyl migrations took place instead of hydrogen migration. The products which are not expected from the reaction sequence mentioned above are suggestive for the study of the nature of aluminum chloride catalysis. The formations of **15** and **16** appear to indicate that the splitting of the phenyl or methoxyphenyl group, isomerization, and a hydride attack to an intermediate carbonium ion occurred. The compound **18** is an isomerization product of **17**.

In a Grignard reaction and a metal hydride (weak nucleophile, *e. g.*, AlH_3 and AlH_2Cl) reduction of epoxides, it is well known that rearrangement to a carbonyl intermediate followed by nucleophilic addition competes with direct nucleophilic ring-opening of epoxide.[12,13] The result presented in this paper is the first example of a Friedel-Crafts type reaction in which the rearrangement to aldehyde followed by condensation has been shown to be the main reaction path.

Experimental

NMR and IR spectra were recorded on a JEOL PMX-60 or a Varian HR-220, and a Hitachi EPI-G2 spectrometers, respectively.

Propylene oxide, 1,2-epoxybutane, and styrene oxide were dried over sodium carbonate and distilled before use. Commercial cyclohexene oxide was used without further purification. Other epoxides were prepared by *m*-chloroperbenzoic acid oxidation of the corresponding olefins. Commercial aluminum chloride (GR grade) was used without further purification. Anisole and nitromethane were dried over sodium hydroxide and phosphorous pentoxide respectively, and distilled before use.

Reaction of Propylene Oxide with Excess Anisole in 1,2-Dichloroethane in the Presence of Aluminum Chloride. To a stirred and cooled (ice bath) solution of 108 g (1.0 mol) of anisole and 14 g (0.11 mol) of aluminum chloride in 200 ml of 1,2-dichloroethane, a mixture of propylene oxide (5.8 g, 0.1 mol) and anisole (54 g, 0.5 mol) was added dropwise during the course of 1.5 h. After 2.0 h, reaction was quenched with 300 ml of water and the organic layer was washed with 100

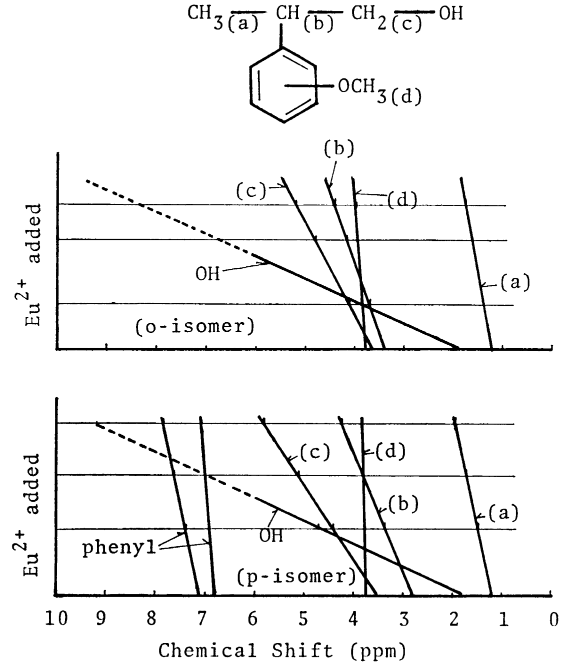


Fig. 1. Paramagnetic shift experiment.

ml of water three times. The combined water layers were extracted with 200 ml of ether three times. The combined organic layers were dried over magnesium sulfate. After removal of the solvents, the product was distilled under reduced pressure: 1st fraction, 70—82 °C/15 mmHg, **3**, **4**, and recovered anisole; 2nd fraction, 0.2 g, 42 °C/5.7 mmHg, phenol; 3rd fraction, 0.7 g, 98 °C/5.0 mmHg, **6**; 4th fraction, 107—111 °C/4.8 mmHg, **5**; 5th fraction, 6.0 g, 140—169 °C/3.2 mmHg, **1**. GLPC analysis showed that the 4th fraction contained 57% and 43% of *o*- and *p*-isomers of **5** respectively together with small amounts of **1** and **6**. To confirm the structure of **5**, a paramagnetic shift experiment in the NMR spectra was carried out using tris(2,2-dimethyl-6,6,7,7,8,8,8-pentafluoro-3,5-octanedionato)europium(III). Results are shown in Fig. 1.

Reaction of Methoxyphenylpropanols with Anisole in the Presence of Aluminum Chloride. In an ice bath, **5** (10 mmol, 70% of *o*-isomer and 30% of *p*-isomer) was treated with anisole (11 g) in the presence of aluminum chloride (20 mmol) for 2 h. After the usual treatments, the reaction mixture was distilled. The yield of a mixture of **1** and **2** (146—172 °C/3.3 mmHg) was 53%. NMR analysis showed that the product contained 20% of **1** and 80% of **2**.

Reaction of Propionaldehyde with Anisole in the Presence of Aluminum Chloride. Propionaldehyde (0.1 mol) was added to anisole (0.2 mol) in 1,2-dichloroethane (300 ml) in the presence of aluminum chloride (0.1 mol) at room temperature for 3.5 h. After the usual work up, 31.7 g of a residual product was obtained. GLPC analysis showed that **1** was formed as a main product, along with many others. Products were separated by column chromatography on silica gel using 30% benzene–hexane.

Reaction of Propylene Oxide with Anisole in the Presence of Aluminum Chloride—Effects of Reaction Conditions. The following example shows a typical experimental procedure. To a solution of anisole (4.33 g) and aluminum chloride (2.7 g) in 1,2-dichloroethane (40 ml) was added 1.33 g of propylene oxide over a period of 2 h at ice-bath temperature. The reaction mixture was stirred at that temperature for an additional 1.5 h. Then the reaction was quenched with a mixture of ice water (50 ml) and concd hydrochloric acid (5 ml). The organic layer was washed with 20 ml of water. The combined water layers were extracted twice with 50 ml of ether and twice with 30 ml. The combined organic layers were dried over magnesium sulfate and distilled to remove the solvent. GLPC analysis of the residual products using dibutyl phthalate as an internal standard showed 785 mg of **1** was formed in this reaction.

Reaction of 1,2-Epoxybutane with Anisole in the Presence of Aluminum Chloride in Nitromethane Solvent. To a mixture of anisole (100 mmol), aluminum chloride (40 mmol), and nitromethane (40 ml) was added a mixture of 1,2-epoxybutane (20 mmol) and nitromethane (20 ml) during the course of 45 min in an ice bath. After an additional 2.5 h, the reaction was quenched as mentioned above. After removal of the solvents, the residual product was purified by chromatography with silica gel, using benzene as an elutant. Distillation of the crude product by a ball-oven apparatus yielded 1.79 g (33.0%) of **9**, bp 169—172 °C/2.5 mmHg. Isomers of the products could be separated by further chromatography using

TABLE 3. ANALYTICAL DATA

Compound	Bp or mp °C	Formula	Calcd		Found		NMR (δ)		
			C%	H%	C%	H%	CH_3O-		-CH(An)$_2$
1 -*p*,*p*[a]	bp 166—172/ 3.2 mmHg	$C_{17}H_{20}O_2$	79.65	7.86	79.90	8.13	3.73		3.72
1 -*o*,*p*[a]					79.86	7.60	3.76	3.74	4.24
2 -*p*,*p*	mp 66.5—68	$C_{17}H_{20}O_2$	79.65	7.86	79.35	7.91	3.74	3.75	
2 -*o*,*p*					79.51	8.03			
2 -*o*,*o*					79.66	8.04			
8 -*p*,*p*	mp 93—95[b]	$C_{17}H_{18}O_2$	80.26	7.13	79.98	7.39	3.77	3.82	
9 -*p*,*p*[a]		$C_{18}H_{22}O_2$	79.96	8.20	79.84	8.10	3.7^2		3.7^7
9 -*o*,*p*[a]					80.19	8.01	3.7^4	3.7^5	4.3^7
10 mixt		$C_{20}H_{26}O_2$	80.49	8.78	80.19	8.75			3.8 (*p*,*p*-), 4.3^5 (*o*,*p*-)
11 -*p*,*p*	mp 97.5—98.5[c]	$C_{22}H_{22}O_2$	82.98	6.96	82.71	7.05	3.7^2		3.2^7 (*o*,*p*-; 4.7^0)
12 -*p*,*p*		$C_{23}H_{24}O_2$	83.10	7.28	82.79	7.49	3.6^8	3.4^5	3.9^3
12 -*o*,*p*							3.7^6	3.4^6	4.6^0
13 mixt		$C_{20}H_{26}O_2$	80.49	8.78	80.52	8.87			3.5^8 (*p*,*p*-), 4.2^2 (*o*,*p*-)
14 mixt	mp 196—199								4.6^5 (*p*,*p*-), 4.7^7 (*o*,*p*-)
15 -*p*	mp 84—85[d]	$C_{21}H_{20}O$	87.46	6.99	87.52	7.06	3.6^8		(3.2^8, d, 1; 4.1^7, t, 2, J=8 Hz)
15 -*o*					87.34	6.78	3.5^8		(3.2^8, d, 1; 4.7^2, t, 2, J=8 Hz)
16 -*p*,*p*[e]	mp 89—91[f]	$C_{22}H_{20}O_2$	83.51	6.37	83.49	6.65			
17 -*p*,*p*		$C_{20}H_{24}O_2$	81.04	8.16	81.27	8.12	3.7^5		3.5^0
17 -*o*,*p*					81.25	8.46	3.7^5	3.7^6	4.1^0
18 -*p*,*p*		$C_{20}H_{24}O_2$	81.04	8.16	81.15	7.86	3.7^0		(2.7^1, s, 2, -C**H**$_2$An)

a) These products were mentioned by V. A. Topchii, S. V. Zavgorodnii, A. I. Bazaeva, and Ya. I. Yashin, *Izv. Vyssh. Uchebn. Zavend., Khim. Khim. Tekhnol.*, **13**, 1755 (1970), from *Chem. Abstr.*, **75**, 76327f (1971). b) Lit, mp 105 °C, F. v. Wessely, E. Kerschbaum, and A. Kleedorfer, *Monatsh.* **73**, 127 (1940), from *Chem. Abstr.*, **35**, 1781^2 (1941). c) Lit, mp 96—97 °C, K. Sisido, K. Okano, and H. Nozaki, *J. Am. Chem. Soc.*, **77**, 4604 (1955). d) Lit, mp 84—85 °C (*p*-isomer) mp 62—64 °C (*o*-isomer), G. Capozzi, G. Melloni, and G. Modena, *J. Chem. Soc., C*, **1970**, 2621. e) This product may be a mixture of *cis* and *trans* isomers. f) Lit, mp 93—94 °C for *cis* isomer, mp 104.5—105.5 °C for *trans* isomer, Z. Rappoport and Y. Apeloig, *J. Am. Chem. Soc.*, **91**, 6743 (1969).

benzene–hexane (1 : 10) as an elutant. Elemental analyses and NMR spectra are shown in Table 3. The mass spectrum of di-*p*-isomer of **9** was: *m*/*e* (rel intensity); 270 (M^+, 18), 227 (100), 121 (45).

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Japan No. 911503.

References

1) A prelimary report of this work was presented at the 30th National Meeting of the Chemical Society of Japan, Higashi-Osaka, April 1974.

2) A. Rosowsky, "Heterocyclic Compounds with Three- and Four-Membered Rings," ed by A. Weissberger, Interscience, New York (1964), Part I, p. 432; A. Schriesheim, "Friedel-Crafts and Related Reactions," Vol. II, Chap. 18, ed by G. A. Olah, Interscience Publishers, New York (1964), p. 543.

3) M. Inoue, T. Sugita, Y. Kiso, and K. Ichikawa, *Bull. Chem. Soc. Jpn.*, **49**, 1063 (1976).

4) T. Nakajima, S. Suga, T. Sugita, and K. Ichikawa, *Tetrahedron*, **25**, 1807 (1969).

5) See, for example, C. D. Nenitzescu and D. A. Isacescu, *Chem. Ber.*, **66**, 1100 (1933).

6) D. L. Ransley, *J. Org. Chem.*, **31**, 3595 (1966); Y. Butsugan, K. Kawase, K. Saheki, M. Muto, and T. Bito, *Nippon Kagaku Kaishi*, **1973**, 2338.

7) S. Masuda, T. Nakajima, and S. Suga, *J. Chem. Soc., Chem. Commun.*, **1974**, 954.

8) Our own results for the reactions of phenylpropanols, which correspond to the phenylchloropropanes reported by Masuda *et al.*,(7) also showed the formation of 1,1-diphenylpropane as a minor component (6%) of the complex products containing 1,2-diphenylpropane (57%), propylbenzene (10%), and 1,1-diphenylpropene (5%). Acetates of the phenylpropanols, corresponding bromides, and allylbenzene gave similar results.(9)

9) M. Inoue, N. Umaki, T. Sugita, and K. Ichikawa, unpublished results.

10) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 768 (1959).

11) J. E. Hofmann and A. Schriesheim, "Friedel-Crafts and Related Reactions," Vol. II, ed by G. A. Olah, Interscience Publishers, New York (1964), Chap. 19.

12) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, New York (1954), p. 961.

13) M. N. Rerick, "Reduction," ed by R. L. Augustine, Marcel Dekker, New York (1968), Chap. 1.

14) Recently Sekiguchi *et al.* proposed a similar reaction sequence for the reaction of styrene oxide with benzene in the presence of aluminum chloride. K. Kimura, Y. Hayami, K. Matsui, and S. Sekiguchi, Abstr. No. 2D18, 32th National Meeting of the Chemical Society of Japan, Tokyo, April 1975.

15) a) D. J. Pasto and C. C. Cumbo, *J. Org. Chem.*, **30**, 1271 (1965); b) R. E. Parker and B. W. Rockett, *J. Chem. Soc., B*, **1966**, 681; c) B. Rickborn and R. M. Gerkin, *J. Am. Chem. Soc.*, **93**, 1693 (1971); d) D. E. Bissing and A. J. Speziale, *ibid.*, **87**, 2683 (1965); e) D. K. Murphy, R. L. Alumbaugh, and B. Rickborn, *ibid.*, **91**, 2649 (1969).